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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,295	09/09/2002	Menachem Rubinstein	RUBINSTEIN=7	2828

1444 7590 10/07/2008

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EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
10/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/070,295	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	GYAN CHANDRA	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9,11,12,15-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9,11,12,15-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that the office action mailed on 7/8/2008 has been vacated in response to Applicant's request for suspending the office action for 3 months filed along with the request for continued examination filed on 5/1/2008.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/1/2008 has been entered.

Status of Application, Amendments, And/Or Claims

The addition of claim 19 and the cancellation of claim 18 have been made of record.

The amendments of claim 9 have been made of record.

Claims 5, 9, 11-12, 15-17 and 19 are pending.

Claims 5, 9, 11-12, 15-17 and 19 are examined on the merit to the extent that they read on the elected invention of VEGF inhibitor – CSC.

Response to Arguments

Claim Rejections-maintained

Claim Rejections - 35 USC § 112-enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 9, 11, 12 and 15-17 stand rejected and claim 19 is rejected under 35 U.S.C. 112, first paragraph-enablement for the reasons of record in pg. 5-10 of the Office Action mailed on 2/13/2006 and in pg. 3-5 of the Office Action mailed on 4/5/2007.

The instant claims are drawn to a method for inhibiting angiogenesis in adipose tissues in mammals comprising administering to a subject a pharmaceutical composition comprising (i) leptin, (ii) a leptin fragment, (iii) a leptin homolog having 90% sequence identity with sequence of leptin, or (iv) a derivative of leptin or leptin homolog which has the activity of leptin, and optionally, an inhibitor of angiogenesis in a suitable dosage, (v) wherein angiogenesis inhibitor is a VEGF inhibitor, (vi) wherein the derivative said derivative has one or more chemical moieties attached to leptin, (vii) wherein said chemical moieties are water soluble polymers, wherein said polymers are polyethylene glycol, and wherein VEGF is absent in the adipose tissue.

Applicants argue (pages 6-7 of Response of 8/1/2008) that (i) the art accepted rat corneal model is an artificial system since leptin is not normally found in the cornea as leptin is produced and present in adipose tissue; (ii) even if leptin promotes angiogenesis in cornea it may not promote angiogenesis in other tissues as it has not been tested; (iii) the corneal model of angiogenesis is used in only experimental biology. They reiterated their arguments (page 7-8) that the addition of leptin to a leptin-deficient (ob/ob) mouse results in angiopoietin 2 and inhibition of angiogenesis in adipose tissue

and that this occurs through Ang-2 gene in the absence of VEGF (the specificatin page 3, lines 16-17; Figure 4 & 7; Example 3). Applicants argue (page 7-8 of Response) that leptin is a potent inducer of angiopoietic factor Ang-2 and that the induction of Ang-2 occurs without the induction of VEGF. Applicants summarize their arguments (page 8-9) by stating that there is no problem of inherency between prior art cited in the rejection and the instant invention, but the big difference is that the present invention shows that leptin has an angiogenesis inhibitory effect in adipose tissue as now being claimed.

Applicants' arguments have been fully considered but they are not persuasive because the instant rejection is not based on the issue that the -ob/-ob KO mouse is not a proper model to study a gene function. The instant rejection is under 35 U.S.C. 112, first paragraph-enablement and as presented in the previous Office Action of 11/2/2007, the specification only teaches an -ob/-ob mouse or adipose tissue in ob-/- mouse where leptin inhibits angiogenesis. Applicants arguments regarding the rat corneal model have been fully considered but they are not persuasive because this model is well accepted art model for studying angiogenesis response (see Kenyon et al., Invest. Ophthalmol. Vis. Sci. 37: 1625-1632, 1996;Park et al., Exp. And Mol. Med. 33: 95-102, 2001; Hui-Chaun et al., World J. Gastroenerolgy, 5:116-118, 1999). Additionally, it is well established in the art that leptin is an inducer of angiogenesis in normal mammal (IDS, Sierra-Honigmann et al, 1998; previously presented, Bouloumie et al., 1998 and previously presented, Cao et al. Proc. Natl. Acad. Sci. 98:6390-6395, 2001). Therefore, one skilled in the art would understand that leptin will induce angiogenesis in nomal

mammal. Regarding applicants' arguments that leptin inhibits angiogenesis in adipose tissue, the specification does not disclose adipose tissue of a normal mammal wherein adminstering leptin inhibts angiogenesis. A number of publications suport that the administration of leptin promotes wound healing which requires angiogenesis (Frank et al, J. Clin. Invest. 106: 501-509, 2000; Sierra-Honigmann (U.S. Pub. No. 2007/0275874 A1). The specification supports that the administration of leptin promotes blood vessel regression in adipose tissue in ob-/o- mice (Figures 2-3). Therefore, one skilled artisan would understand that leptin administration in ob-/- mice would inhibit angiogenesis in adipose tissue of ob/ob mice. However, the state of the art and lack of support in the instant disclosure provide guidance to one of the skill in the art to conclude that leptin would prmote angiogeneis including in adipose tissue of normal mammals, unless evidence to contrary.

Regarding Applicants' arguments that leptin administration to a leptin-deficient (ob/ob) mouse results in angiopoietin-2 and inhibition of angiogenesis in adipose tissue and that this occurs through Ang-2 gene in the absence of VEGF have been fully considered and they are persuasive with regard to the inhibition of angiogenesis in ob/ob mice. However, the claims are drawn to a method for inhibiting angiogenesis in any mamal and thefore, the instant invention is not enabled to its full scope. Additonally, claim 19 requires that VEGF is absent, and the speficfication does not disclose that VEGF is absent in normal mammals. Holms and Zachary (Genome Biol. 6: 209-209.10, 2005) teach that VEGF family proteins are present in normal animals and they can be detected from embryonic day 7 (page 209.6, Localization and function).

Therefore, claim 19 is only enabled for ob-/- mice, unless evidence to contrary. Appplicants' arguments that leptin is potent inducer of angiopoietic factor Ang-2 have been fully considered and they are found persuasive with respect to leptin mediated induction of Ang-2. But merely the presence or overexpression of a single gene (i.e., Ang-2) may not be the only factor that could control a complex process such as angiogenesis. Additionally, the role of Ang-2 is not just the inhibition of angiogenesis, but it is more in vascular homeostatisis (see Teichert-Kuliszewska et al, Cardiovascular Res. 49: 659-670, 2001). Teichert-Kuliszewska et al is not applied as a prior art, but applied to support the state of the art. Therefore, in view of the state of the art and for the reasons discussed above, the instnt rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GYAN CHANDRA whose telephone number is (571)272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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21 September 2008
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/Robert Landsman/
Primary Examiner, Art Unit 1647